PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.01.2005
Applicant's or agent's file reference WPP286463	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/04314	07.10.2003	09.10.2002

Applicant
NEUROPHARMA, S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
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Authorized Officer

Ambroa, J R/
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Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WPP286463	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/04314	International filing date *(day/month/year)* 07.10.2003	Priority date *(day/month/year)* 09.10.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/473		
Applicant NEUROPHARMA, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.05.2004	19.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Cortés, J Telephone No. +49 89 2399-8206

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/04314

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-56 as originally filed

Claims, Numbers

1-12 received on 26.05.2004 with letter of 24.05.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12

   because:

   ☒ the said international application, or the said claims Nos. 12 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-6
	No:	Claims	1, 2, 7-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the opinion

With letter of 24.05.2004 the Applicant has filed an amended claim set, wherein the claimed subject-matter has been restricted to the group of inventions 1 identified in the search report. Therefore the amended claim set complies with the requirement of unity of invention (Rule 13.1 PCT).

Additionally a proviso has been introduced at the end of claim 1 in order to exclude two specific prior art compounds disclosed e.g. in D4 and D5. D4 and D5 do not disclose the alleged pharmacology or medical use of the present compounds and can therefore be regarded as so-called "accidental disclosures".

A definition for the group E has been introduced. The basis for this amendment can be found on page 9 of the description.

Therefore the amendments comply with the requirements of Article 34(b) PCT.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 12 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion with regard to the industrial applicability will be formulated for this claim (Article 34(4)(a)(i) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: HU, MING-KUAN ET AL: "Homodimeric Tacrine Congeners as Acetylcholinesterase Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, 26 April 2002 (2002-04-26), pages 2277-2282, XP002267304

D2: CASTRO ET AL: "Peripheral and Dual Binding Site Acetylcholinesterase Inhibitors: Implications in treatment of Alzheimer's Disease" MINI REVIEWS IN MEDICINAL CHEMISTRY, vol. 1, 2001, pages 267-272, XP001157056

D3: WO 01/17529 A (UNITECH PHARMACEUTICALS INC (US)) 15 March 2001 (2001-03-15)

D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOUSSEF, KHAIRIA M.: "Synthesis and pharmacological screening of certain substituted tetrahydropyrido[4,3-b]quinolines and pyrazolo[4,3-c]quinolines" XP002267190 retrieved from STN Database accession no. 136:118414

D5: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOUSSEF, KHAIRIA M. ET AL: "Synthesis and pharmacological screening of certain substituted tetrahydropyrido [4,3-b] quinolines and pyrazolo [4,3-c] quinolines" XP002267193 retrieved from STN Database accession no. 125:1080

Novelty (Article 33(2) PCT)

D3 discloses compounds which fall within the claimed scope (D3: e.g. compounds 8a-c, page 4, example 13).

The present claims 1, 2 and 7-12 are therefore not novel.

The present compounds differ from the compounds in D1 and D2 in the radical X. The compounds of D4 and D5 have been excluded by the proviso.

Inventive Step (Article 33(3) PCT)

D1 to D3 disclose structurally related AchE-Inhibitors for the treatment of Alzheimer's disease. D3 can be regarded as the closest prior art.

The problem of the present invention was the provision of further AChE inhibitors for the treatment of Alzheimer's disease.

Since D3 discloses compounds of the alleged pharmacology within the claimed scope, the present invention lacks an inventive step.

Clarity (Article 6 PCT)

The amended claim 1 lacks a definition of R12.